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(54) Title: ANTICONVULSANT COMPOSITIONS AND METHOD

(57) Abstract

Compositions and methods for controlling seizures with compositions containing diphenylhydantoin and/or dextromethorphan or another compound that binds to the same sites in the brain as dextromethorphan.

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ANTICONVULSANT COMPOSITIONS AND METHOD

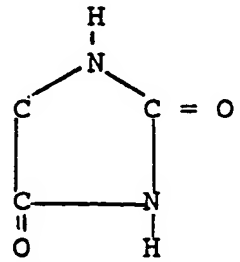
Field of the Invention

This invention relates to a group of novel compositions containing diphenylhydantoin and/or dextromethorphan or another compound that binds to the same sites in the brain as dextromethorphan, with substantially the same or higher affinity. Another aspect of this invention relates to the use of these compositions as anticonvulsants, and to methods for controlling seizures using these compositions.

Background of the Invention

Most types of epileptic seizures, including induced generalized or focal seizures, except absence seizures, can be treated and prevented with diphenylhydantoin (DPH), which is also commonly called phenytoin, and other antiepileptic hydantoins.

DPH has the following structural formula:



DPH usually exerts antiepileptic activity without causing general depression of the central nervous system. It can limit the development of maximal seizure activity and reduce the spread of the seizure process from an active focus.

Antiepileptic preparations containing DPH (and other antiepileptic hydantoins) are available in solid (oral) and

liquid (oral and injectable) forms; they contain from 30 to 250mg of DPH per unit dose.

The effectiveness of DPH increases with dosage. However, DPH is also toxic. Most of its toxic effects increase with dosage and length of exposure, and vary with the mode of administration.

Dose-dependent toxic effects associated with chronic use of DPH and other hydantoins include cerebellar vestibular effects (nystagmus, ataxia, diplopia, vertigo, etc.) and other central nervous system disturbances (blurred vision, mydriasis, hyperactive tendon reflexes, etc.), behavioral changes (hyperactivity , confusion, dullness, drowsiness and hallucinations), increased frequency of seizures, peripheral neuropathy, gastrointestinal distress, gingival hyperplasia, osteomalacia, megaloblastic anemia (that can be fatal), hirsutism, endocrine effects, lymphdenopathy et al. At very high doses (especially when administered intravenously), DPH can also cause cardiovascular collapse and/or general depression of the central nervous system.

DPH is not the only antiepileptic drug. A variety of other antiepileptic agents are known. Unfortunately, many of them also have undesirable toxic and side effects. Moreover, most known antiepileptic agents are effective for only selective types of seizures.

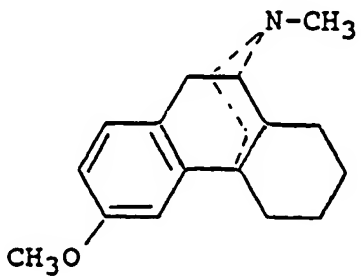
Accordingly, there is a need in the field for development of an anticonvulsant agent that would cause as few and as mild toxic and side effects as possible and yet be effective against a wide variety of seizure types. More specifically, there is a need for an anticonvulsant agent that would be effective at doses that minimize dose-related side effects against a variety of seizures.

In Mol. Pharmacol., 23:619-628 and 23:629-640 (1983) Craviso, G.L. and Musacchio, J. M. reported that dextromethorphan (DM), a non-narcotic, nonaddictive, antitussive agent, had distinct binding sites in the central nervous system, which were different from the binding sites for opiate compounds. The same investigators found that the binding of DM was effec-

tively inhibited in vitro by a number of non-narcotic centrally active antitussives (including certain DM analogs), certain phenothiazine neuroleptics, as well as some other compounds such as selective antidepressants, antihistamines, and muscarinic agents (i.e. agents that bind to the nuscarinic receptor). They also found that the in vitro binding of DM to the central nervous system was markedly increased in the presence of certain compounds such as DPH and noscapine, but they were unable to predict which compounds would enhance DM binding and which would not. The authors proposed that research be conducted to determine whether DPH is an antitussive (or whether DM is an anticonvulsant), but that statement is at best a proposal for experimentation and does not suggest the method or the compositions of the present invention. Specifically, the anticonvulsant activity of DM can not be deduced or suggested from the disclosure of these references. In addition, the fact that DPH increases the binding of DM does not suggest that one would potentiate activity of the other, much less that DM would potentiate DPH activity.

It has now been discovered that DM and several other compounds that bind to the same sites in the brain possess substantial anticonvulsant activity in vivo. More important, it has been unexpectedly discovered that DM and these other compounds vigorously potentiate the anticonvulsant activity of DPH in vivo when administered simultaneously (or consecutively) with DPH. As a result, the minimum effective does of DPH (and consequently its dose-dependent side-effects) can be substantially decreased. The potentiating effect is present even at subthreshold levels of DM (or the other compounds that bind to the same CNS sites).

Dextromethorphan (D-3-methoxy-N-methylmorphinan) has the following structural formula:



It is sold as an antitussive in various liquid, resin, and solid antitussive dosage forms containing from 5 to 30 mg/5 ml of DM (or the equivalent), together with alcohol and/or other carriers and active ingredients used in management of cough and other symptoms of the common cold.

Although DM is a potent antitussive, it has no analgesic or addictive properties. Unlike codeine to which it is structurally related, it rarely produces drowsiness or gastrointestinal disturbances and has low toxicity (Goodman & Gilman's, The Pharmacological Basis of Therapeutics, Sixth Ed., MacMillan Publishing Co., New York 1980).

Therefore, use of DM (and other relatively innocuous compounds that compete with DM for the same CNS binding sites) to potentiate DPH will result in a substantial decrease in the dose-and exposure-dependent side effects of DPH with a concomitant enhancement (or without a compromise) in anti-seizure activity.

Objects of the Invention

Accordingly, it is an object of this invention to provide a method for controlling seizures in mammals, and particularly clinical epileptic seizures.

Another object of this invention is to provide pharmaceutical formulations comprising an effective amount of anticonvulsant agents useful for inhibiting, preventing, or controlling epileptic seizures.

Another object of the invention is to provide pharmaceutical compositions that have anticonvulsant activity similar or superior to that of DPH, at lower doses than DPH, said compositions having substantially less toxicity and fewer side effects than DPH.

These and other objects of the invention will be apparent to one of ordinary skill in the art in light of the present description, appended claims and accompanying drawings.

Brief Description of the Drawings:

Figure 1 is a bar diagram showing the duration of tonic forelimb extension as a function of the amount of anticonvulsant agent administered.

Figure 2 is a bar diagram showing the presence of seizure activity, as a function of the amount of anticonvulsant administered.

Figure 3 is a semilog plot of the doses at which a given anticonvulsant composition controls seizure activity of a percentage of the subjects tested.

Figure 4 is a semilog plot of the doses at which a given anticonvulsant composition limits the duration of tonic forelimb extension.

Summary of the Invention

One aspect of the present invention is directed to an anticonvulsant composition comprising as an active ingredient an amount of a compound selected from the group consisting of dextromethorphan and non-narcotic, nonaddictive, low-toxicity compounds that bind to the same central nervous system sites as dextromethorphan with at least about the same affinity for said sites, said amount being effective for controlling seizures in mammals.

Another aspect of the present invention is directed to an anticonvulsant composition comprising as active ingredients (a) an antiepileptic hydantoin or noscapine, and (b) a compound selected from the group consisting of dextromethorphan and other non-narcotic, nonaddictive, low-toxicity compounds that bind to the same central nervous system sites as dextromethorphan with at least about the same affinity for said sites; wherein the amount of the active ingredients in combination is effective for controlling seizures in mammals, and the amount of said compound is at least sufficient to potentiate said hydantoin or noscapine.

Still other aspects of the present invention are directed to dosage forms comprising amounts of the aforementioned compositions effective for controlling seizures in mammals.

Yet another aspect of the present invention relates to a method for controlling seizures in a mammal in need of such treatment comprising administering to said mammal an amount effective for controlling seizures of a compound selected from

the group consisting of dextromethorphan and non-narcotic, nonaddictive, low-toxicity compounds that bind to the same sites in the central nervous system as dextromethorphan with at least about the same affinity for said sites as dextromethorphan.

Another aspect of the present invention relates to a method for controlling seizures in a mammal in need of such treatment comprising administering to said mammal an amount of an antiepileptic hydantoin (or noscapine) and an amount of dextromethorphan or another non-narcotic, nonaddictive, low-toxicity compound that binds to the same central nervous system sites as dextromethorphan with at least about the same affinity, said amounts in combination being effective for controlling seizures in said mammals, said amount of DM or said other compound being at least sufficient to potentiate DPH.

Detailed Description of the Invention

The present inventors have discovered that the non-opiate antitussive DM and several other compounds that bind to the same central nervous system (CNS) site as DM with at least about the same affinity are effective anticonvulsant agents and also potentiate the anticonvulsant action of DPH and other antiepileptic hydantoins, thus substantially lowering the minimum effective dose of DPH, and other hydantoins. As a result, the amount of hydantoin necessary for antiepileptic activity in a given case is substantially lower than that which would have been effective for the same purpose, if the hydantoin had been used alone.

Any one of a number of nonaddictive, non-narcotic compounds of low toxicity that effectively compete with DM for the same central nervous system binding sites could be used to potentiate DPH. Such compounds include but are not limited to non-opiate antitussives that bind to the same CNS sites as DM. Specific examples of compounds that can be used in the compositions of the present invention include benztropine, chlorpromazine, perphenazine, fluphenazine, trifluoperazine, prochlorperazine, alpha-flupenthixol, trimeprazine, dimethoxanate, opipramol, promethazine, pipazethate, carbetapentane, carami-

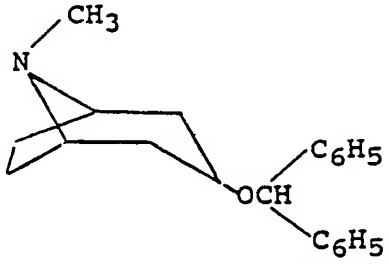
phen, and noscapine as well as pharmaceutically acceptable derivatives, homologs, isomers, analogs and organic and inorganic addition salts thereof having therapeutic activity as provided herein. For example, the DM analogs that have the groups-$CH_2(CO)CH_3$ and $CH_2CH(CH_3)OH$ instead of CH_3 as N-position substituents can be used. The methylsulfonate salt of benztropine, the hydrochloride and ethanedisulfonate salts of caramiphen, the citrate salt of carbetapentane, the maleate and hydrochloride salts of chlorpromazine, the dihydrochloride salt of flupenthixol and fluphenazines are some examples of the forms of the above compounds that can be used in the compositions of the present invention.

Preferred are perphenazine, fluphenazine, trifluoperazine, opipramol, and carbetapentane with DM being most preferred. These compounds have anticonvulsant activity independent of their DPH-potentiating action.

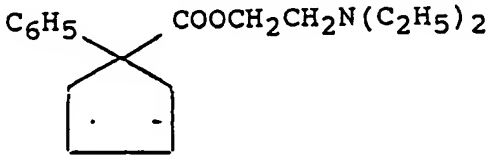
The structural formulas and IUPAC names of these compounds are given in Table I below.

TABLE I

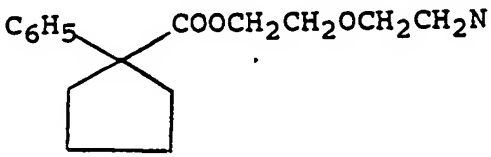
benztropine: 3-(diphenylmethoxy)-8-methyl-8-azabicyclo[3.2.1] octane



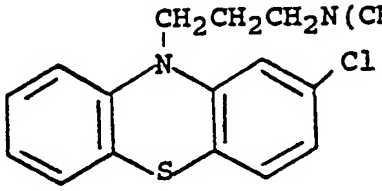
caramiphen: 1-phenylcyclopentanecarboxylic acid 2-(diethylamino)ethyl ester



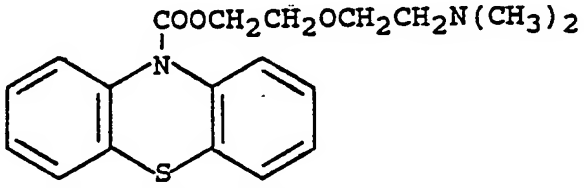
carbetapentane: 1-phenylcyclopentanecarboxylic acid 2-(2-diethylaminoethoxy)ethyl ester



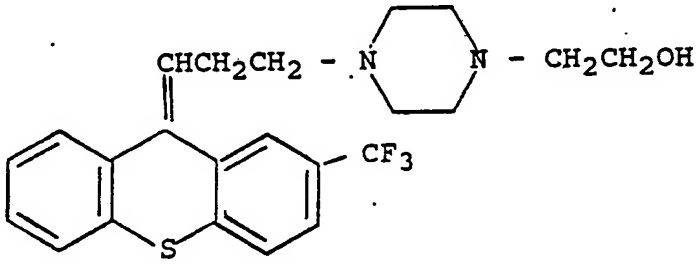
chlorpromazine: 2-chloro-N,N-dimethyl-10H-phenothiazine-10-propanamine



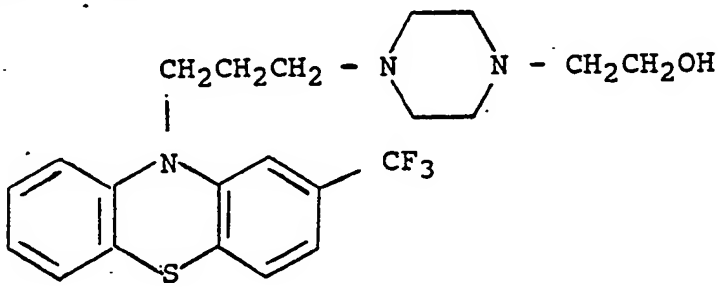
dimethoxanate: 10H-phenothiazine-10-carboxylic acid 2-[2-(dimethylamino)ethoxy]ethyl ester



flupenthixol: 4-[3-[2(trifluoromethyl)-9H-thioxanthen-9-ylidene]propyl]-1-piperazineethanol



fluphenazine: 4-[3-[2-(trifluoromethyl)-10H-phenothiazin-10-yl]propyl]-1-piperazineethanol



opipramol: 4-[3[(5H-dibenz[b,flazepin-5-yl)propyl]-1-piperazineethanol

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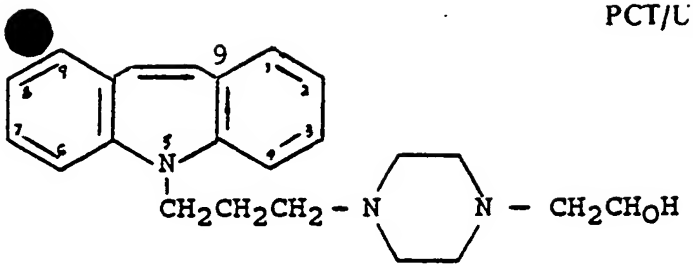
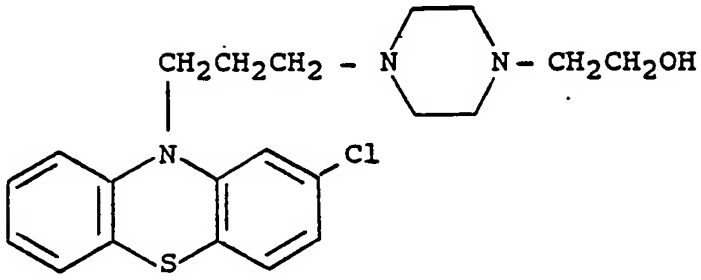
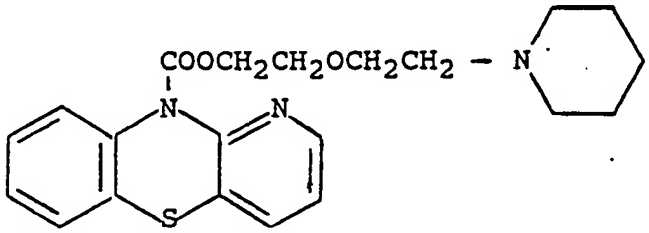


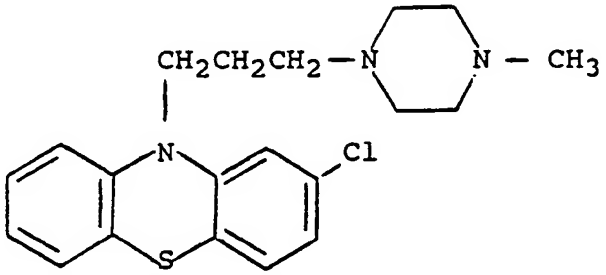
perphenazine: 4-[3-(2-chlorophenothiazin-10-yl)propyl]-1-piperazineethanol



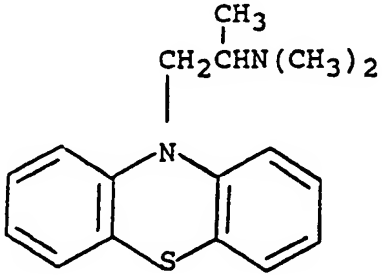
pipazethate: 10H-pyrido[3,2-b][1,4]benzothiadiazine-10-carboxylic acid 2-(2-piperidinoethoxy)ethyl ester



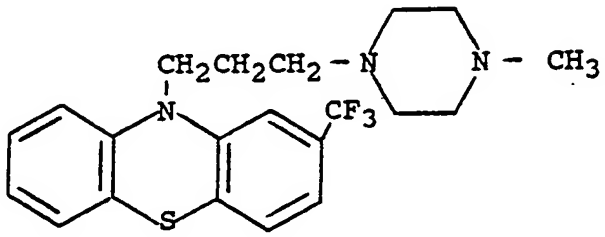
prochlorperazine: 2-chloro-10-[3-(4-methyl-1-piperazinyl)propyl]-10H-phenothiazine



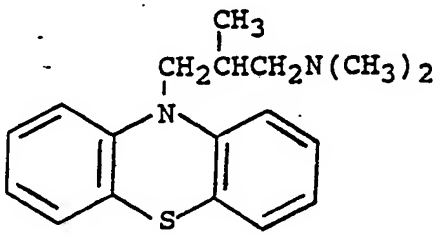
promethazine: N,N,alpha-trimethyl-10H-phenothiazine-10-ethanamine



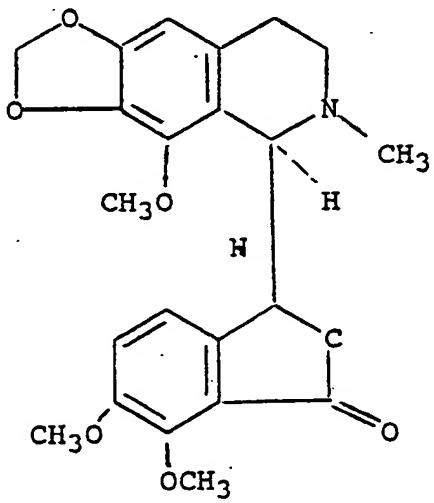
trifluoperazine: 10-[3-(4-methylpiperazin-1-yl)-propyl]-2-(trifluoromethyl)-10H-phenothiazine



trimeprazine: 10-[3-(dimethylamino)-2-methylpropyl]phenothiazine



noscapine: 6,7-dimethoxy-3-(5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-g]isoquinolin-5-yl)-1(3H)-isobenzofuranone



The above compounds can be obtained from commercial sources such as:

DPH: Polychemicals Laboratories, Bronx, New York
DM: Hoffman-La Roche, Nutley, N.J.
benztropine: Merck Sharp and Dohme West Point, Pa.

carbetapentane: CM/K&K Life Sciences Group, Cleveland, Ohio
flupenthixol: Smith Kline French, Philadelphia, PA
opipramol: Ciba-Geigy, Summit, N.J.
mephenytoin: Sandoz Pharmaceuticals, Inc., East Hanover, N.J.
ethotoin: Abbott Laboratories, North Chicago, IL
noscapine: Mallincrodt Pharmaceutics, St. Louis, MO

or can be synthesized using well-known techniques, such as described in U.S. Patents No. 2,409,754; U.S. Pat. No. 2,595,405; Swiss Pat. No. 234,452; British Pat. No. 753,799; U.S. Pat's No. 2,404,588; No. 2,645,640; No. 2,778,824; British Pat. No. 925,538; U.S. Pat. No. 3,194,733; Swiss Pat's No. 359,143 and No. 360,061; U.S. Pat. No. 2,860,138; No. 2,989,529; No. 2,902,484; No. 2,530,451 and No. 2,607,773; No. 2,921,069; No. 2,837,518; No. 2,676,177; and No. 3,108,106, the disclosure of which is incorporated by reference herein. In addition to DPH, other antiepileptic hydantoins can be advantageously potentiated by DM and compounds that bind to the same brain sites. These include mephenytoin, N-demethylated mephenytoin, and ethotoin. However, DPH is preferred.

The compositions of the present invention can be administered orally or parenterally (subcutaneously or intravenously because intramuscular injection is not indicated for DPH-containing compositions).

In the case of potentiated DPH compositions, it is not essential that DPH and the potentiating compound be administered simultaneously or in the same dosage form. Sequential administration is acceptable. However, simultaneous administration is preferred.

The active ingredients in the oral dose are preferably administered in the form of a tablet, pill, capsule or other solid dosage unit. Coating of the tablet or protective capsule is desirable to facilitate swallowing or to prevent unpleasant taste. Suitable coatings may be prepared from aqueous suspension containing sugar and insoluble powders such as starch, calcium carbonate, talc or titanium dioxide suspended with a suitable mixing agent such as gelatin. Film coatings consisting of water-soluble or dispersible materials such as hydroxypropylmethylcellulose, cellulose, methylcellulose, carboxy-

methylcellulose, and mixtures of cellulose acetate phthalate and polyethylene glycol applied out of aqueous or nonaqueous solvents are suitable for coating the tablets and pills made according to the present invention. Soft shell gelatin capsules of the type normally used as pharmaceutical coatings are also suitable as dosage forms for the invention. Of course, the capsules may comprise any well-known pharmaceutically acceptable material such as gelatin, cellulose derivatives or the like.

The active ingredients of the present invention may be compounded in the desired oral form in combination with inert ingredients including fillers such as talc, lactose, starch, bentonite, diatomaceous earth, lubricants and food flavorings. Tablets for use in the present invention may be made by punching or compressing the active ingredients and the fillers in a tabletting machine.

Liquid oral doses in the form of solutions and suspensions are also suitable for use in the present invention as are suppositories for rectal administration. In making solutions and suspensions, the active ingredients may be dissolved or suspended in distilled water containing a small amount of alcohol to facilitate hydantoin suspension, conventional U.S.P. syrup formulations and any other pharmaceutically acceptable carrier liquid.

For parenteral administration the compounds of the invention are dissolved in a pharmaceutically acceptable injectable carrier liquid. A preferred carrier liquid for DPH includes polypropylene glycol and alcohol in water (pH:12 by addition of NaOH) and would be a suitable carrier for the potentiated compositions of the present invention.

When used as anticonvulsants in mammals, the compositions of the present invention containing DM (or one or more of the compounds that bind to the same site) can generally be administered at a dosage level from about 15 to about 200 milligrams and preferably from about 30 to about 150 milligrams of active ingredient two or three times a day.

The potentiated compositions containing DPH can gen-

erally be administered at a dosage level of DPH ranging from about 50 to about 500 mg per day for adults (preferably about 100 to 300 mg) and from about 1 to about 8 mg of DPH per kg body weight/ day for children.

In these potentiated DPH-containing compositions, the amount of DPH necessary for effectiveness is usually substantially lower than it would have been if DPH had been used alone to control the epilepsy. The amount of the potentiating compound should be at least sufficient to potentiate the DPH i.e. at least sufficient to lower the minimum effective dose of DPH. The noscapine doses are comparable to the ones given for DPH.

Although subthreshold levels of the potentiating compound have sufficient potentiating activity when used in conjunction with DPH, the potentiated compositions of the present invention are not limited to containing subthreshold levels of the potentiating compound.

The daily effective dosage, or the dosage required to prevent or inhibit or control convulsions from a particular disease or stimulant depends on the condition being treated, the individual characteristics of each mammal being treated and the nature of the physical or chemical stimulus inducing or responsible for the convulsive activity. Thus, the exact dose required to alleviate convulsions attributable to a particular disorder or stimulus or their effects will vary within the range discussed above from one patient to another and is subject to optimization, which can be carried out by conventional and convenient experimental techniques.

Solid pharmaceutical dosage forms such as pills, capsules, or tablets may contain from about 40 to 300 milligrams of active ingredient, or combination of active ingredients. More specifically, such dosage forms may contain from about 15 to 200 mg of DM (or other potentiating compound) and from about 25 to 100 mg of DPH (or other hydantoin).

The liquid oral dosage forms of the present invention are preferably administered in the form of a solution or suspension in a pharmaceutically acceptable vehicle. Liquid

dosages containing from about 9 to about 60 milligrams of active ingredient (or combination of active ingredients) per cubic centimeter of vehicle are useful in administering these agents to mammals.

The liquid parenteral dosage forms of the present invention may contain from about 9 to about 60 mg/of active ingredient or combination of active ingredients per ml of vehicle.

Suppository dosage forms may be prepared by incorporating an active agent into a base material that can be formed into the desired shape. Suitable base materials include cocoa butter, glycerinated gelatin, hydrogenated vegetable fats, mixtures of polythethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol. Suppositories for adults may contain from about 40 to about 300 milligrams of active ingredient or combination of active ingredients.

The invention is further described below by reference to specific examples, which are intended to illustrate the invention without limiting its scope.

EXAMPLES:

The anticonvulsant activity of the instant compositions was measured by inducing maximal electroshock seizures (MES) in rats using the following standard testing conditions:

Animals. Male, Sprague Dawley rats (200-300 g from Zivic Miller, Alison Park, PA) were used for all experiments. Upon delivery, the animals were housed individually in a temperature-controlled room with a standard 12-hour light-dark cycle (lights on 0600 hr to 1800 hr). Food and water were available ad libitum.

Maximal electroshock seizures (MES). Supramaximal (tonic extension of the hindlimbs) seizures were induced electrically by means of a Wahlquist shock apparatus (Wahlquist Inst., Salt Lake City, Utah) with a built-in high internal resistance designed to provide a constant current across animals. A 60-Hz, 50 mA current was delivered transauricularly for 2.0 seconds via small alligator clips attached to the pinna of each ear. This current intensity elicited complete tonic

extension of the hindlimbs in at least 90% of control rats. Two measures of seizure severity were recorded for each MES seizure; the duration of tonic forelimb extension (TFE) and the presence or absence of tonic hindlimb extension (THE). For the MES test, rats were placed in a clear rectangular plastic cage (45 x 25 x 12 cm) with the top open, permitting full view of the animals' motor response to the seizure.

In preliminary studies ethosuximide (400 mg/kg, s.c.) a drug which is known to prevent tonic extension of maximal tonic extension threshold seizures but is ineffective against MES seizures (Piredda et al, 1985 J. PET 232:741 (1985), was also found ineffective against MES seizures in these Examples. Therefore, the shock parameters used here clearly induce MES, and not threshold, seizures. Throughout the study, all animals were used only once.

Experimental protocol. Each rat received a single subcutaneous (s.c.) injection of dextromethorphan (DM, n=10 per group) or diphenylhydantoin (DPH, n=10 per group). At various times postinjection, the animals were subjected to an MES seizure and tested as described above. The duration of action for each drug was determined over a two-hour period. Dose-response studies for DM (15, 20, 25, and 30 mg/kg) and DPH (3.125, 6.25, 12.5, 25.0, and 50 mg/kg) were subsequently carried out at the time of maximal effect, i.e. 30 minutes postinjection. In separate groups of rats, a subthreshold effective does of DM (15 mg/kg) was administered simultaneously with DPH (1.56, 2.125)= and 6.25 mg/kg). Thirty minutes later the animals were exposed to a single MES seizure and the response measured. The method of Litchfield and Wilcoxin J. PET 96:99 (1949) was used to determine the ED_{50} values and 95% confidence limits for each drug tested, as well as for the combination of DM and DPH. Potency comparisons were made using the computer program No. 10 by Tallarida and Murray (Manual of Pharmacologic Calculations, Springer Verlag, New York, 1981).

Results. The administration of DM and DPH resulted in a time- (Fig. 1 and 2) and dose- (Fig. 3 and 4) related decrease in the duration of TPE and blockage of THE. Maximal

anticonvulsant effect occurred with 15-30 minutes following DM administration and within 30-60 minutes following the injection of DPH, with significant anticonvulsant action still evident two hours later (Fig. 1 and 2). The anticonvulsant ED_{50} (95% CL) for the effect of DM to block THE was 24.1 mg/kg (19.7-29.5) (Fig. 3). The tests show DM to be only 3 times less potent than DPH as an anticonvulsant in the rat. In addition, the simultaneous administration of a subthreshold dose of DM (15 mg/kg) increased the potency of DPH (Fig. 3 and 4), lowering the anticonvulsant ED_{50} for DPH threefold to 2.79 mg/kg (14.4-5.43) in the MES test (Fig. 3). In fact, additional preliminary tests indicate that DM is able to increase the potency of DPH more than three-fold.

At the time of testing, the DM- and DM/DPH-treated animals exhibited normal exploratory behavior when placed in the novel testing environment. There were no signs of overt sedation, ataxia or motor impairment at any time after drug administration.

The above results indicate that the co-administration of DM and DPH has a synergistic effect in that the former (even at subthreshold levels) potentiates the latter. A three-fold decrease of the ED_{50} of DPH would significantly lower the incidence and severity of its side effects.

WHAT IS CLAIMED IS:

1. An anticonvulsant composition comprising as an active ingredient an amount effective for controlling seizures in mammals of a compound selected from the group consisting of dextromethorphan and other non-narcotic, non-addictive, low-toxicity compounds that bind to the same central nervous system sites as dextromethorphan.

2. A composition according to claim 1 wherein said other compounds bind to the same sites as dextromethorphan with at least about the same affinity.

3. A composition according to claim 2 wherein said active ingredient is selected from the group consisting of dextromethorphan, benztropine, caramiphen, carbetapentane, chlorpromazine, dimethoxanate, flupenthixol, fluphenazine, opipramol, perphenazine, pipazethate, prochlorperazine, promethazine, trifluoperazine, trimeprazine, and noscapine and pharmaceutically acceptable homologs, isomers, organic and inorganic addition salts thereof.

4. A composition according to claim 2, wherein said other compounds are selected from the group consisting of non-opiate antitussives.

5. A composition according to claim 2, wherein said active ingredient is dextromethorphan.

6. A composition according to claim 2, wherein said active ingredient is perphenazine.

7. A composition according to claim 2, wherein said active ingredient is fluphenazine.

8. A composition according to claim 2, wherein said active ingredient is trifluoperazine.

9. A composition according to claim 2, wherein said active ingredient is opipramol.

10. A composition comprising an effective amount for controlling seizures in a mammal of a combination of an anti-epileptic hydantoin and a compound selected from the group consisting of dextromethorphan and other non-narcotic, non-addictive, low toxicity compounds that bind to the same central nervous system sites as dextromethorphan with at least about

the same affinity, wherein the amount of said compound is at least sufficient to potentiate said hydantoin.

11. A composition according to claim 10, said other compounds binding to the same central nervous system suites as dextromethorphan with at least about the same affinity for said sites as dextromethorphan.

12. A composition according to claim 11, wherein the amount of said hydantoin is substantially lower than that which would display the same seizure-controlling activity if said hydantoin had been used as the sole active ingredient.

13. A composition according to claim 11, wherein said hydantoin is diphenylhydantoin.

14. A composition according to claim 12, wherein said hydantoin is diphenylhydantoin.

15. A composition according to claim 13, wherein said compound is selected from the group consisting of dextromethorphan, benztropine, caramiphen, carbetapentane, chlorpromazine, dimethoxanate, flupenthixol, fluphenazine, opipramol, perphenazine, pipazethate, procholrperazine, promethazine, trifluperazine, trimeprazine, and noscapine, and pharmaceutically acceptable homologs, derivatives, isomers, analogs and organic an inorganic addition sales thereof.

16. A composition according to claim 11, wherein said other compounds are selected from the group consisting of non-opiate antitussives.

17. A composition according to claim 13, wherein said combination is of diphenylhydantoin and dextromethorphan.

18. A composition according to claim 17, wherein said dextromethorphan is used at a subthreshold level.

19. A composition according to claim 15, wherein said compound is selected from the group consisting of perphenazine, fluphenazine, trifluoperazine and opipramol.

20. A composition according to claim 19, wherein the amount of said diphenylhydantoin is substantially lower than that which would display the same seizure-controlling activity, if diphenylhydantoin were used as the sole active ingredient.

21. A composition according to any one of claims 2-4,

11, 13, 16, and 17, contained in a liquid injectable dosage form.

22. A composition according to any one of claims 2-4, 11, 13, 16, and 17, contained in a solid oral dosage form

23. A composition according to any one of claims 2-4, 11, 13, 16, and 17, contained in a liquid oral dosage form.

24. A method for controlling seizures in a mammal in need of such treatment comprising administering to said mammal an effective amount for controlling seizures of a compound selected from the group consisting of dextromethorphan and other non-narcotic, nonaddictive, low-toxicity compounds that bind to the same central nervous system site as dextromethorphan with at least about the same affinity.

25. A method according to claim 24, said compound being selected from the group consisting of dextromethorphan, benztropine, caramiphen, carbetapentane, chlorpromazine, dimethoxanate, flupenthixol, fluphenazine, opipramol, perphenazine, pipazethate, prochlorperazine, promethazine, trifluoperazine, trimeprazine, and noscapine and pharmaceutically acceptable homologs, isomers, and organic and inorganic addition salts thereof.

26. A method according to claim 24, wherein said compound is selected from the group consisting of dextromethorphan, its pharmaceutically acceptable isomers, derivatives, analogs, homologs, organic and inorganic addition salts, and its derivatives containing $-CH_2(CO)CH_3$ and $-CH_2CH(CH_3)OH$ as N-position substituents.

27. A method according to claim 24, wherein said compound is selected from the group consisting of non-opiate antitussive compounds that bind to the same central nervous system sites as dextromethorphan with at least about the same binding affinity.

28. A method according to claim 24, wherein said compound is dextromethorphan.

29. A method according to claim 24, wherein said compound is selected from the group consisting of perphenazine, fluphenazine, trifluoperazine and opipramol.

30. A method for controlling seizures in a mammal in need of such treatment comprising administering to said mamma; an amount of,

(a) an antiepileptic hydantoin, and

(b) an antiepileptic hydantoin-potentiating amount of a compound selected from the group consisting of dextromethorphan and other non-narcotic, non-addictive, low-toxicity compounds that bind to the same central nervous system sites with at least about the same affinity as dextromethorphan, said amounts in combination being effective for controlling seizures in said mammal.

31. A method according to claim 30, wherein said hydantoin is diphenylhydantoin.

32. A method according to claim 31, wherein said compound is selected from the group consisting of dextromethorphan, benztropine, caramiphen, carbetapentane, chlorpromazine, dimethoxanate, flupenthixol, fluphenazine, opipramol, perphenazine, pipazethate, prochlorperazine, promethazine, trifluoperazine, and trimeprazine, and pharmaceutically acceptable homologs, isomers, organic and inorganic addition sales thereof.

33. A method according the claim 31, wherein said compound is dextromethorphan.

34. A method according to claim 31, wherein said amount of said diphenylhydantoin is substantially lower than that which would display the same seizure-controlling activity, if diphenylhydantoin alone had been administered.

35. A composition according to claim 31, wherein the amount of said compound is at least sufficient to potentiate said diphenylhydantoin.

36. A composition according to claim 32, wherein said compound is selected from the group consisting of perphenazine, fluphenazine, trifluoperazine and opipramol.

37. A composition according to claim 31, wherein said diphenyldantoin and said compound are co-administered.

38. A composition according to claim 29, wherein said compound and said diphenylhydantoin are administered successively.

39. A composition comprising an effective amount for controlling seizures in a mammal of a combination of noscapine and a compound selected from the group consisting of dextromethorphan and other non-narcotic, non-addictive, low-toxicity compounds that bind to the same central nervous system site as dextromethorphan with at least about the same affinity as dextromethorphan, wherein the amount of said compound is at least sufficient to potentiate said noscapine.

40. A composition according to claim 39, wherein said compound is dextromethorphan.

41. A method for controlling seizures in a mammal in need of such treatment comprising administering the said mammal an amount of

(a) noscapine and

(b) a noscapine-potentiating amount of a compound selected from the group consisting of dextromethorphan and other non-narcotic, non-addictive, low-toxicity compounds that bind to the same central nervous system sites with at least about the same affinity as dextromethorphan, said amount in combination being effective for controlling seizures in said mammal.

42. A method according to claim 41 wherein said compound is dextromethorphan.

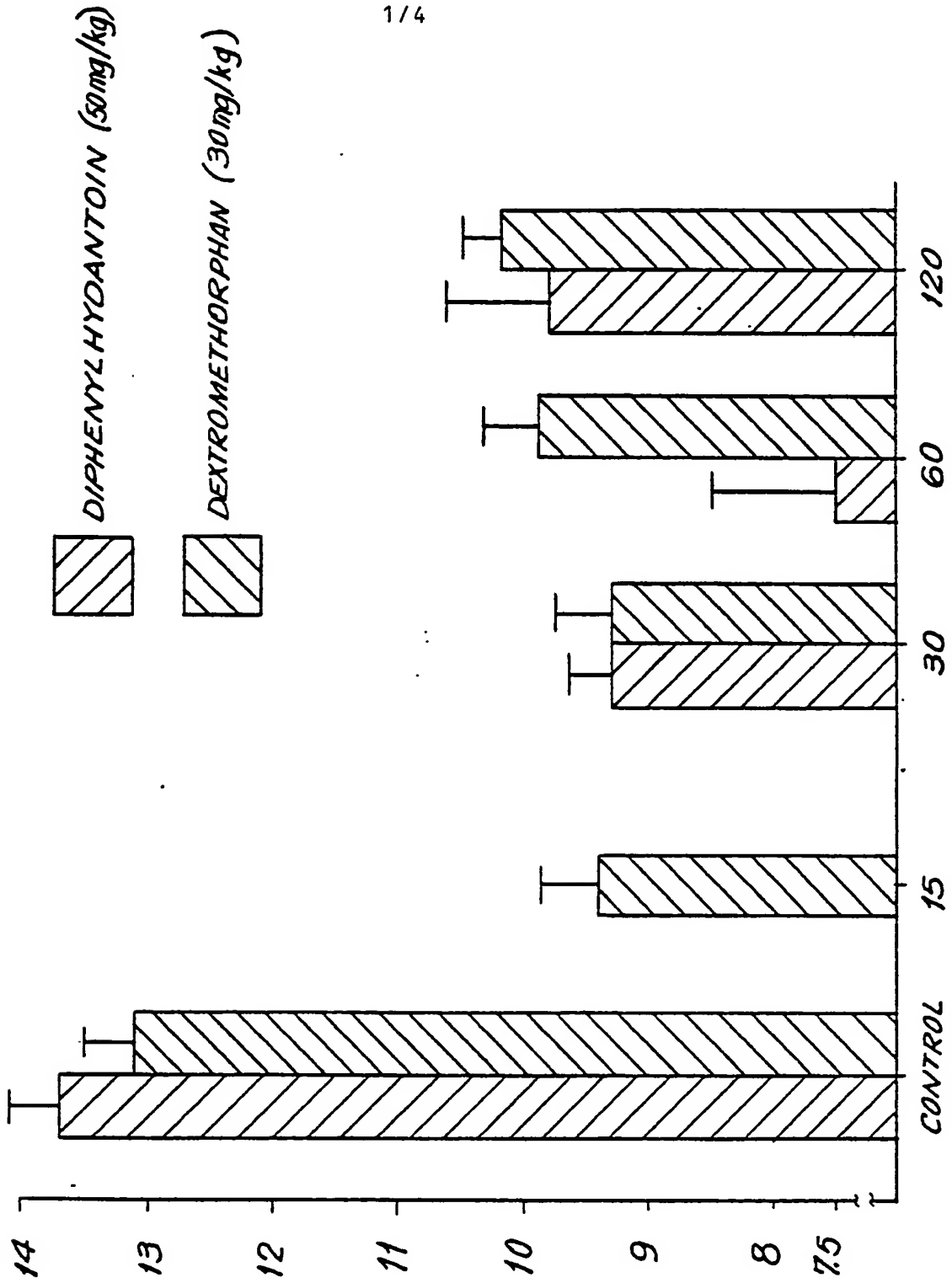

DIPHENYLHYDANTOIN (50mg/kg)
DEXTROMETHORPHAN (30mg/kg)
CONTROL
15
30
60
120
14
13
12
11
10
9
8
7.5
DURATION OF TFE
(SECONDS ± S.E.)

FIG. 1

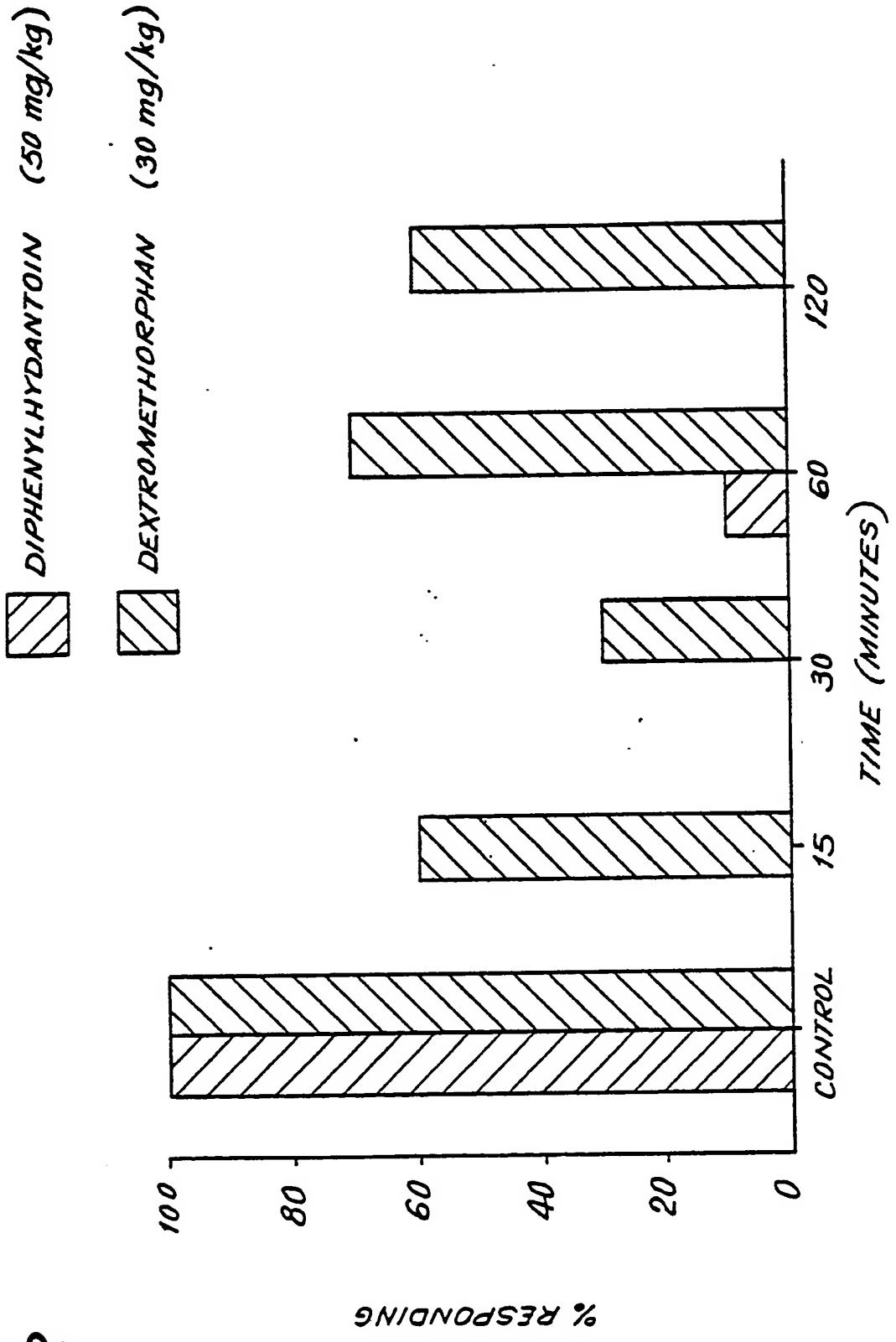

DIPHENYLHYDANTOIN (50 mg/kg)
DEXTROMETHORPHAN (30 mg/kg)
% RESPONDING
100
80
60
40
20
0
CONTROL
15
30
60
120
TIME (MINUTES)

FIG. 2

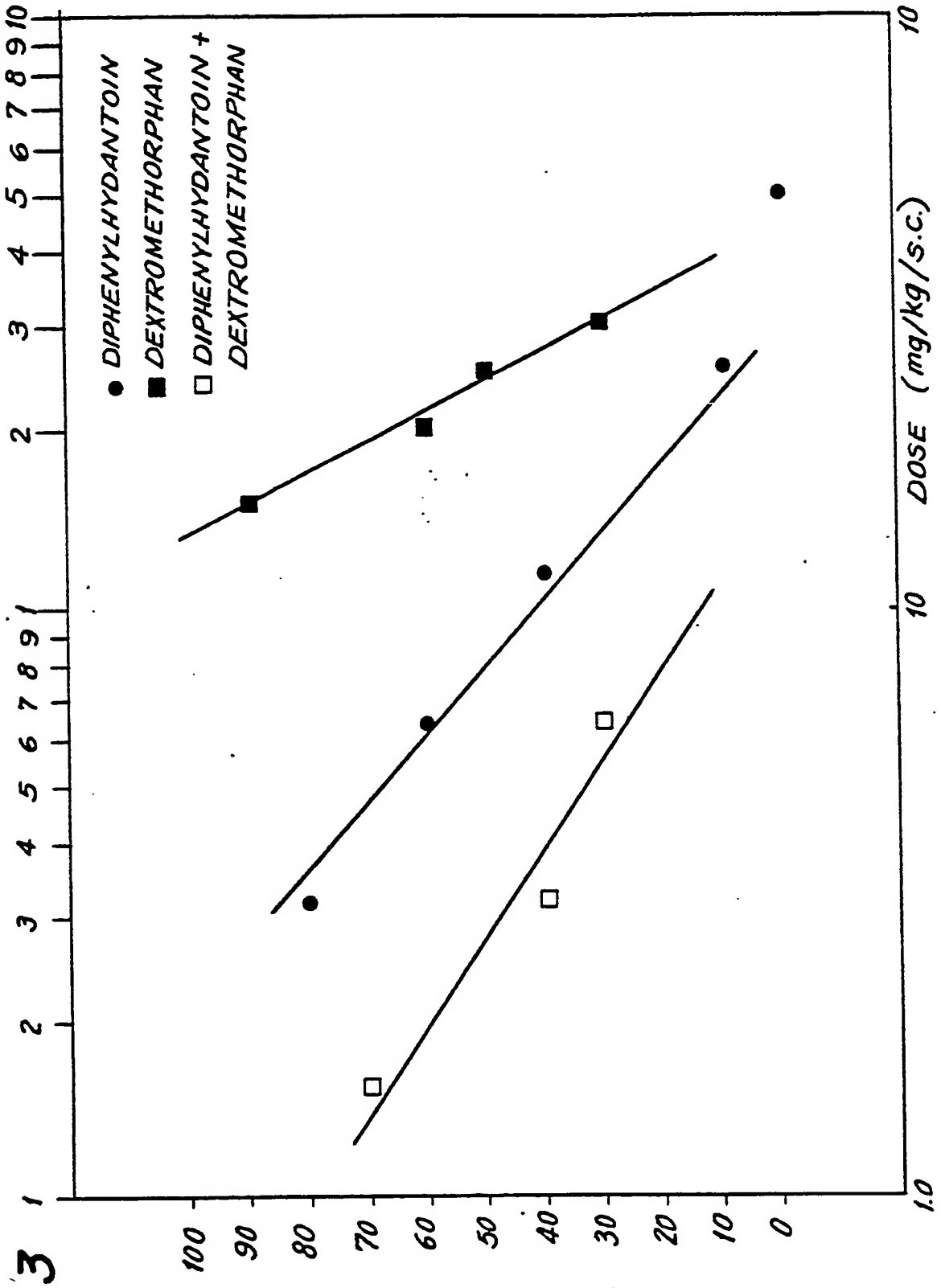
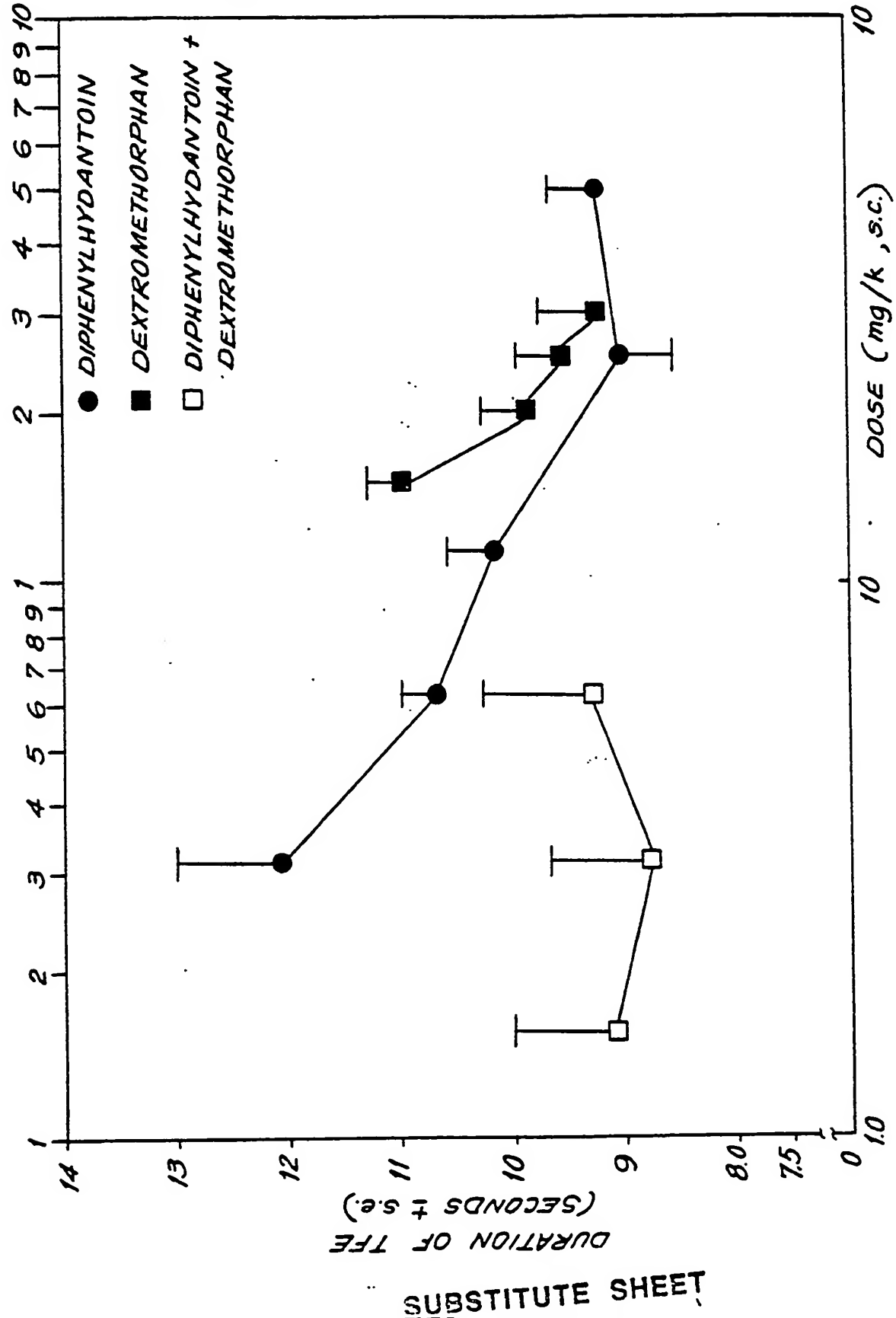

DIPHENYLHYDANTOIN
DEXTROMETHORPHAN
DIPHENYLHYDANTOIN + DEXTROMETHORPHAN
% RESPONDING
100
90
80
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
8
9
10
DOSE (mg/kg/s.c.)
1.0

FIG. 3

FIG. 4


DIPHENYLHYDANTOIN
DEXTROMETHORPHAN
DIPHENYLHYDANTOIN + DEXTROMETHORPHAN
DURATION OF TFE (SECONDS ± S.E.)
DOSE (mg/k, s.c.)
14
13
12
11
10
9
8.0
7.5
1
2
3
4
5
6
7
8
9
10
1.0

INTERNATIONAL SEARCH REPORT

International Application No PCT/US86/01629

I. CLASSIFICATION F SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A61K 31/24,31/44,31/47,31/54,31/55,31,235,31/415,31/495

U.S.: 514/217,223,255,282,307,311,389,532 and 537

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	514-217,223,255,282,306,311,389,532 and 537

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [6]

CAS ONLINE

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X	Chemical Abstracts, Volume 99, No. 3, issued 18 July 1983, (Columbus Ohio, USA), Craviso et al, "High-affinity dextromethorphan binding sites in guinea pig brain.", see page 63 column 2, the abstract No. 16449h, Mol. Pharmacol. 1983, 23(3) 629-40 (Eng).	1-5,21-25,27-28,and 39-40
X	Chemical Abstracts, Volume 94, No. 21, issued 25 May 1981. (Columbus Ohio, USA). Kleinrok et al, "Effect of dopaminergic and GABA-ergic drugs given alone or in combination on the anticonvulsant action of phenobarbital and diphenylhydantoin in the electroshock test in mice," see page 62, column 1, the abstract No. 167770d, (Inst. Clin. Pathol., Med. Sch. Lublin, Pol). Epilepsia (N.Y.) 1980, 21(5), 519-29 (Eng).	1-4,7,21-25,27,29,30-32 and 34-39

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [3]	Date of Mailing of this International Search Report [3]
16 Sept 1986	10 OCT 1986
International Searching Authority [1]	**Signature of Authorized Officer [20]**
ISA/US	Stanley Friedman

III. DOCUMENTS C NSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No [18]
X	Chemical Abstracts, Volume 89, No. 19, issued 06 Nov. 1978, (Columbus Ohio, USA). Varma, "Simultaneous gas chromatographic determination of diphenylhydantoin, carbamazepine (tegretol), phenobarbital and primidone in presense of kemadrin (procyclidine) and prolixin (fluphenazine) in plasma of psychiatric patients." see page 6, column 2, the abstract No. 157,073m, J. Chromatogr. 1978, 155(1), 182-6(Eng).	1-4,7, 21-25, 27,29, 30-32 and 34-39
X	Goodman and Gilman's "The Pharmacological Basis of Therapeutics, 6th Edition, 1980, Macmillan Publishing Co., Inc. New York, see pages 448-456 and 528-530, entire disclosure	1-5,10-28,30-35 and 31-38